

the effect of compounds 1h and 126 on erbB-2 and Grb2 association in MDA453 cells; Figure 18b depicts the effect of compounds 3a and 5b on erbB-2 and Grb2 association in MDA453 cells; and Figure 18c depicts the effect of compound 1i on erbB-2 and Grb2 association in MDA453 cells.

- 5 Figure 19 depicts a reaction scheme for the preparation of compound 20a. (a) NaHMDS, trisyl azide, THF, -78°C, 73%; (b) LiOH, H₂O₂, THF-H₂O, 92%; (c) HOBt, DIPCDI, DMF, 70%; (d) Ph₃P, THF-H₂O, reflux, quantitative; (e) Ac₂O, Et₃N, DCM, 80%; (f) (PCy₃)₂Cl₂Ru=CHPh, DCM, reflux; (g) (PCy₃)(IMes)Cl₂Ru=CHPh, toluene, 80°C.

- Figure 20 depicts a reaction scheme for the preparation of compounds 223-224. (a) 10 for 109: Fmoc-Gly-OH, HOBt, DIPCDI, DMF, 89%; for 210: Fmoc-Ile-OH, HOBt, DIPCDI, DMF, 86%; for 211: Fmoc-Aib-OH, HOBt, DIPCDI, DMF, 88%; for 212: FMoc-1-amino-cyclohexane carboxylic acid, HOBt, DIPCDI, DMF, 82%; (b) Piperidine, DMF, quantitative; (c) HOBt, DIPCDI, DMF, 82% (217); 81% (218); 78% (219); 76% (220); (d) (PCy₃)₂Cl₂Ru=CHPh, DCM, reflux; 63% (221); 67% (222); (e) TFA-TES-H₂O, 15 quantitative.

Figure 21 depicts a reaction scheme for the preparation of compounds 232-233. (a) NaHMDS, BrCH₂CO₂^tBu, THF, -78°C, 77%; (b) LiOH, H₂O₂, THF-H₂O, 85%; (c) HOAt, EDCI, DMF, 85% (227); 75% (228); 72% (229); (d) (PCy₃)₂Cl₂Ru=CHPh, DCM, reflux; 83% (230); 87% (231); (e) TFA-TES-H₂O, quantitative.

- 20 Figure 22 depicts a reaction scheme for the preparation of compound 239. (a) allylmagnesium bromide, CuBr·Me₂S, THF, -78°C, 83%; (b) H₂O₂, LiOH, THF-H₂O, 90%; (c) HOBt, EDCI, DMF, 79%; (d) (PCy₃)₂Cl₂Ru=CHPh, DCM, reflux; 77%; (e) TFA-TES-H₂O, quantitative.

- Figure 23 depicts a reaction scheme for the preparation of compound 246. (a) 10% 25 Pd/C, H₂, EtOAc, quantitative; (b) NaHMDS, BrCH₂CO₂^tBu, THF, -78°C, 78%; (c) H₂O₂, LiOH, THF-H₂O, 86%; (d) HOAt, EDCI, DMF, 82%; (e) TFA-TES-H₂O, quantitative.

Figure 24 depicts the extracellular ELISA GrB2 SH2 domain binding assay on compounds 126, 1i, 3a, 5b, 1h, and 233. The IC₅₀ values are as follows: 126 (0.003); 1i (0.18); 3a (6.00); 5b (1.8); 1h (0.003); and 233 (0.002).

- 30 Figure 25 depicts the whole cell (intracellular) assay of GrB2 binding to p185erbB-2. Figure 25A depicts the effect of compounds 233 and 126 on erbB-2 and Grb2 association in MDA453 cells (IP: GrB2 C-23 WB: PTy(PY99) and Grb2). Figure 25B depicts the effect of

6/12/08